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Hepatology Snapshot:

Mechanisms of liver fibrosis resolution

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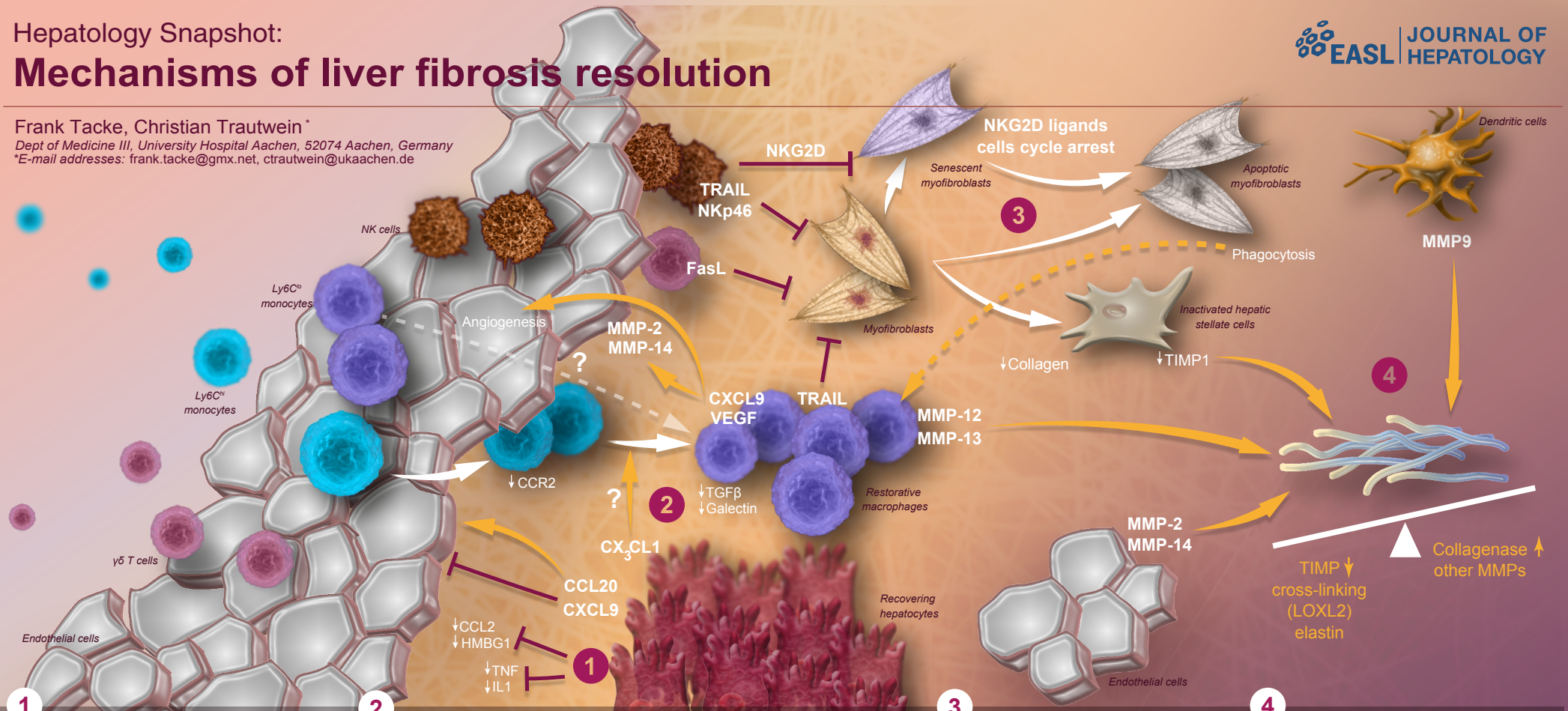

1 Cessation of chronic damage

The mechanisms of liver fibrosis progression and regression are mainly studied in experimental mouse models, which allow targeted interventions. Although it became evident from mouse models and human samples that restorative mechanisms are co-induced during ongoing injury as well, one of the key factors for tipping the balance towards fibrosis resolution is the cessation of chronic liver injury. While this is usually achieved in patients by successful suppression of hepatitis B or C virus replication or withdrawal from toxins such as alcohol [2], fibrosis regression is rapidly initiated in mouse models of fibrosis within days after termination of chronic injury such as toxin administration (e.g., carbon tetrachloride, thioacetamide), cholestasis (e.g., reversion of bile duct ligation) or metabolic challenge (e.g., methionine-choline deficient diet) [3]. Chronic injury is associated with the release of (pro-inflammatory) danger signals (e.g., HMGB-1, free DNA), activation of inflammatory signaling cascades in hepatocytes (e.g., NF-κB or JNK) and the release of manifold cytokines and chemokines, these processes cease upon termination of liver damage [4].

2 Shifting the intrahepatic balance from inflammation to restoration

Recovering hepatocytes and their neighboring non-parenchymal cells switch the microenvironment from a pro-inflammatory milieu to resolution, so that restorative and anti-inflammatory mediators become dominant. As a consequence, the chemokine-mediated attraction of inflammatory monocytes (via CCR2) or NKT cells (via CXCL16) from the circulation but also the activation of intrahepatic and bypassing T cells is dramatically reduced [5], allowing the intrahepatic immune cells to adjust their phenotype. One of the most prominent phenotypic switches is observed for macrophages that acquire a restorative phenotype, characterized by low Ly6C expression in mice and high expression of matrix metalloproteinases (MMP), growth factors (favoring hepatocyte recovery) and phagocytosis-related receptors [6]. Interestingly, the phagocytosis of apoptotic myofibroblasts and/or hepatocytes might further promote the differentiation of macrophages towards restorative cells [6].
Liver fibrosis regression is also accompanied by increased numbers of dendritic cells (DCs) and NK cells in the liver [7]. While DCs favor matrix degradation via expression of MMP-9 [7], NK cells induce the apoptosis of activated and senescent myofibroblasts via NKG2D and TRAIL [1,8]. In addition, gamma delta T cell receptor expressing T cells (γδ T cells) also induce myofibroblast apoptosis via Fas/FasL interactions [9].
Some recent studies provided new insights into the role of angiogenesis for fibrosis resolution. While angiogenesis is regularly observed in progressing fibrosis [10], sinusoidal angiogenesis might be a requirement for optimal fibrosis regression [11]. Pro-angiogenic factors like vascular endothelial growth factor (VEGF) or the chemokine CXCL9 from myeloid cells have been identified as important functional contributors to fibrosis resolution in mouse models [11,12].

3 Deactivation and elimination of myofibroblasts

The main collagen producing cells in the liver are hepatic stellate cells (HSC) that transdifferentiate into myofibroblasts [13]. The deactivation of myofibroblasts is key to fibrosis regression, and three mechanisms have been proposed: senescence, apoptosis and inactivation. Senescence describes a phenotype of myofibroblasts with reduced fibrogenic gene expression and cell cycle exit, which confers susceptibility to NK cell mediated apoptosis [14]. Driven by the withdrawal of anti-apoptotic signals as well as by NK, γδ T and possibly also CD8+ cytotoxic T cells, myofibroblasts undergo apoptosis during fibrosis regression [1,15]. Moreover, probably around half of the myofibroblasts become inactivated and revert to a "quiescent-like" HSC phenotype, but these inactivated HSC remain "primed", meaning that they can more easily be reactivated to become myofibroblasts upon fibrogenic stimuli [16,17].

4 Extracellular matrix degradation

The ultimate step for achieving reversibility of fibrosis is the degradation of the excessive extracellular matrix. The most important degrading effectors are MMPs, which consist of a family of enzymes with different substrate affinities to matrix components [18]. Besides releasing anti-inflammatory mediators, restorative macrophages provide such fibrolytic mediators, especially MMP12 and MMP13 [6], but also neutrophils and HSC can express different MMPs [18]. However, some features of advanced fibrosis confer a relative resistance to matrix degradation; these features include collagen cross-linking and deposition of elastin [1].

Keywords: Liver fibrosis regression; Macrophages; Myofibroblasts; Hepatic stellate cell; Matrix degradation.
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Key facts

The successful treatment of chronic liver diseases such as viral hepatitis has provided compelling clinical evidence that liver fibrosis is, in principle, reversible. Mouse models of liver fibrosis regression are critical to define the essential cellular and molecular pathways for liver fibrosis resolution (see Figure).

Mechanisms of liver fibrosis resolution

The figure summarizes cellular and molecular mechanisms identified in animal models of liver fibrosis resolution. Important steps mediating the reversibility of liver fibrosis are the cessation of chronic damage (allowing hepatocyte recovery and modulating the microenvironment), shifting the balance from inflammation to resolution (leading to phenotypic adjustments of immune cells, especially induction of restorative macrophages), deactivation of myofibroblasts (by senescence, apoptosis and inactivation) and, finally, matrix degradation (reflected by an altered balance between matrix stabilizing and matrix degrading factors).

Liver fibrosis is the typical response to chronic liver disease and characterized by the massive excess of extracellular matrix in the liver. Nowadays, liver fibrosis is viewed as an evolutionary conserved wound healing response to tissue injury, which is primarily driven by inflammatory and immune mediated mechanisms [1]. Importantly, liver fibrosis is not a unidirectional progressive process, ultimately leading to liver cirrhosis and organ failure, but is in principle reversible. A large body of clinical evidence, especially from patients effectively treated for chronic hepatitis B or C virus infections, suggest that regression from hepatic fibrosis occurs in liver disease patients, if the underlying liver injury is resolved or successfully treated [2]. This prompted intense basic research on the molecular and cellular mechanisms of liver fibrosis regression, intending to translate these findings into new therapies targeting such restorative pathways in human liver disease. These mechanisms can be roughly divided into four steps (see Figure), although we would like to emphasize that these pathways do not necessarily represent subsequent events but can be partially or fully activated also independent from each other.

Therapeutic targeting of fibrosis resolution

Understanding the cellular and molecular mechanisms of liver fibrosis regression prompted extensive research on new pharmacological approaches to augment these mechanisms. All of the above mentioned steps are currently investigated in preclinical and/or early clinical trials as potential targets (reviewed in [13,19]): (1) reduce or control tissue injury (e.g., by blocking apoptosis of hepatocytes); (2) transfer of bone-marrow derived restorative macrophages or inhibition of inflammatory monocyte infiltration (e.g., by blocking chemokine receptor CCR2 [cenicriviroc] or its ligand CCL2); (3) increase myofibroblast apoptosis (e.g., via CB1 antagonist [rimonabant], 5HT antagonist or IFNγ directed to HSC); (4) increase matrix degradation by inhibiting the collagen cross-linking enzyme lysyl oxidase homologue 2 (e.g., via simtuzumab) or inhibiting TIMPs, the natural matrix metalloproteinase (MMP) antagonists. The rapid progress in understanding mechanisms of liver fibrosis resolution raises realistic hopes for effective antifibrotic therapies in the near future [13].

Conclusions

Important mechanisms for the reversibility of liver fibrosis are the cessation of chronic damage (allowing hepatocyte recovery and modulating the microenvironment), shifting the balance from inflammation to resolution (leading to phenotypic adjustments of the immune cells, especially induction of restorative macrophages), deactivation of myofibroblasts (by senescence, apoptosis and inactivation) and, finally, matrix degradation (reflected by an altered balance between matrix stabilizing and matrix degrading factors).

Abbreviations: CCL/CXCL, chemokine; CX3CL1, fractalkine; FasL, Fas ligand (CD95L); HMBG-1, High-Mobility-Group-Protein B1; IL, interleukin; LOXL2, lysyl oxidase homologue 2; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of MMP; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

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Conflict of interest

Frank Tacke has received funding and has served as a scientific advisor on fibrosis research for Noxxon (Berlin, Germany) and Tobira Therapeutics (San Francisco, CA) and Christian Trautwein for Astra Zeneca (Mölndal, Sweden) and Bayer (Berlin, Germany).

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